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MAJOR ARTICLE

Risk of cancer in people with HIV experiencing varying degrees of immune recovery with sustained virological suppression on antiretroviral treatment for more than 2 years: an international, multicentre, observational cohort

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Background: The impact of long-term virological suppression and CD4 count recovery on non-AIDS defining cancers (NADC) is unclear. We determined whether poor immune recovery was associated with incident cancer risk in people with HIV with virological suppression (VS).

Methods: Participants from the D:A:D and RESPOND collaborations in Europe and Australia who achieved ≥2 years of VS on ART between Dec 1999 and Dec 2022 were included. Follow-up was from baseline (date of VS for two years) until the earliest of a first cancer event, virological failure, final follow-up, or administrative censoring date. Multivariable Poisson regression was used to assess associations between cancer incidence (overall, AIDS-defining cancer (ADC), NADC, infection-related, infection-unrelated) and time-updated CD4 count stratified by pre-ART nadir CD4 counts.

Results: Overall, 48,343 people with VS were included (median [IQR] baseline age 43 years [37-50], CD4 count 540 cells/μL [380-730], nadir CD4 count 245 cells/μL [121-394], 74% male). There were 1,933 incident cancers, median 6.2 years [2.9-9.5] (incidence rate (IR): 6.43 [95%CI 6.15-6.73]/1000 person-years). Higher time-updated CD4 count was associated with a reduced risk of overall cancer (adjusted incidence rate ratio [aIRR] for time-updated CD4 350-499: 0.45 [95%CI 0.39-0.51]; 500-749: 0.30 [0.27-0.34], and ≥750: 0.26 [0.23-0.30] vs. <350 cells/μL, p<0.0001). There was a significant reduction in all cancers risk by higher time-updated CD4 count regardless of nadir CD4 count, with higher pre-ART nadir CD4 count exhibiting lower risk.

Conclusions: Despite VS on ART for more than two years, people with poorer immune recovery experience a significantly higher incidence of cancer.

Keywords: Cancers; Non-AIDS-defining cancers; Immune recovery; virological suppression; People with HIV.

Key Points : Using data from RESPOND/D:A:D cohorts, we demonstrated a significant association between poor immune recovery with risk of cancers in people with sustained virological suppression. The findings emphasise the importance of early ART initiation and early implementation of cancer screening strategies.

BACKGROUND

The landscape of morbidity and mortality has evolved in people with HIV, shifting from opportunistic infections and cancer associated with immunodeficiency to age-associated conditions such as cardiovascular disease, , and non-AIDS cancers (NADC).[1-3] Many age-associated conditions are associated with immune dysregulation of aging; persistent immune activation and inflammation.[4] This phenomenon is observed in people with HIV who are virologically suppressed on antiretroviral therapy (ART). While the risk of AIDS-defining cancer (ADC) falls with higher CD4 counts, the association with NADC incidence is less clear, especially once individuals have achieved VS.[5, 6] Persistent immunosuppression (CD4 count <200 cells/μL), is associated with increased long-term mortality and NADC mortality,[7] while reduced mortality rates are observed in those with CD4 counts >500 cells/μL.[8]

Previous studies have shown that either lack of HIV virological suppression or failure to restore CD4 counts are associated with increased risks of infection-related and infection-unrelated cancers.[9, 10] A low CD4/CD8 ratio, an indicator of immune senescence and activation, has been associated with ADC, NADC and certain cancers.[11, 12] However, these studies generally included individuals regardless of virological suppression and examined the association between viral load or CD4 counts with cancer risk separately. It is unknown whether incomplete CD4 recovery with sustained virological suppression is associated with increased risk of NADC.

Using data from the combined RESPOND and D:A:D studies with large numbers of people and long-tern follow-up we assessed whether poor immune recovery despite virological suppression is an independent predictor of incident cancers.

METHODS

Study design

The D:A:D and RESPOND cohorts are prospective, multi-cohort collaborations from across Europe and Australia, comprising approximately 49,000 people with HIV from 11 cohorts in D:A:D (1999-2016), and 35,000 people from 17 cohorts in RESPOND (2017-ongoing). Data from both cohort studies were merged, with some participants being part of, and providing data to, both collaborations. For individuals enrolled in both collaborations, data was used from the D:A:D study until the baseline date of rollover into the RESPOND study after which data were used from RESPOND. Full details of both studies have been published.[13, 14] In both studies, cancer events

are documented using study-specific case report forms; prospective events are centrally validated against pre-defined algorithms by study clinicians at the coordinating center and reviewed by an external oncologist.[15]

Study population

We included all participants aged 18 years or older with a CD4 count and viral load (VL) available from 1 year prior to and 12 weeks after D:A:D/RESPOND cohort entry (Supplementary Figure S1, exclusion box 1), prior to assessment of eligibility for this study. We excluded participants with no VL after cohort entry, or at least 2 years of follow-up for those who were ART-naïve at cohort entry. We defined study baseline as the date of the first VL <200 copies/mL after ≥2 years of continuous virological suppression (a minimum of 2 VL within 2 years was required), from the latest of cohort entry or 1 January 2006 in D:A:D, and from the latest of local cohort entry or 1 January 2012 in RESPOND. Participants were required to have ≥1 CD4 count available in addition to the baseline measurement, ≥1 CD4 count in the year prior to the cancer event diagnosis, and an average of one CD4 count each two years of follow-up to the cancer event or last visit (Supplementary Figure S1, exclusion box 2). Individuals with cancers prior to baseline were also excluded.

Study exposure and outcomes

The main exposure of interest was time-updated CD4 count (categorized as <350, 350-499, 500-749 and ≥750 cells/μL). We partitioned follow-up into 6-month intervals to update CD4 counts throughout the study. The primary study outcome was incident cancers overall (excluding pre-cancer dysplasia, non-melanoma skin cancers, relapse), and incident cancers separately for ADC, NADC, infection-related, infection-unrelated, smoking-related, and obesity-related cancers.[11, 15] These cancer groups are not mutually exclusive since each cancer type could be included in more than one category (Supplementary Table S1).

Statistical analysis

We summarized baseline participant characteristics by cancer status. Follow-up was from baseline to the first date of a cancer event, virological failure (VL>200 copies/mL), discontinuation of ART for >2 months, or the last cohort date, whichever occurred first. Last cohort date was defined as 6 months after the last clinic visit or cohort administrative censor date (1 Feb 2016) in D:A:D; or final follow-up date or administrative censor date (31 Dec 2021) in RESPOND. The final follow-up in RESPOND was defined as the latest of the most recent CD4 count, VL measurement, drop out date, or date of death. We excluded participants from RESPOND cohorts with low event reporting, defined as those with upper 95% CI for cancer incidence was below the overall RESPOND incidence. For participants with sustained virological suppression prior to cohort entry the baseline date was the date of study entry within the respective cohort.

Crude and adjusted incidence rates (and 95% confidence intervals [CI]) of cancers overall and each cancer group were calculated. We used Poisson regression with robust standard errors to investigate the association between the incidence of cancers and time-updated CD4 count categories, adjusted for potential confounders, chosen a *priori*. These included sex/gender, race/ethnicity, geographical region, HIV mode of acquisition, viral hepatitis C infection (HCV), hepatitis B infection (HBV), body mass index (BMI), smoking (never, current, previous or unknown), hypertension, diabetes, dyslipidemia, and a prior non-cancer AIDS event, end stage liver and kidney disease, cardiovascular disease, or chronic kidney disease, all fixed at baseline to mitigate any potential mediating effects on the time-updated CD4 counts. Age (per 10-year increase), and any exposure to ART were fitted as time-updated variables. In these models, any exposure to ART was defined as a time-updated binary variable.

We stratified results by key subgroups: age group, race/ethnicity, and pre-ART CD4 nadir. We tested interactions between time-updated CD4 count and age (categorized as ≤50, >50 years), sex and calendar periods (≤2015, >2015) in the fully adjusted model. Tests for interactions were limited to cancers overall to ensure sufficient power. We also conducted subgroup analyses for the association of time-updated CD4 count and cancer risk for sex (male and female), age group (≤50, >50 years) and pre-ART CD4 nadir (<200, 200-350, >350 cells/μL). Due to collinearity between nadir CD4 count and time-updated CD4 count, both variables were not included in the same multivariable regression model. To explore the association between time-updated CD4 and cancer risk by baseline immune status, we conducted stratified analyses across nadir CD4 categories.

We included change in CD4 count (calculated as the change in time-updated CD4 count from baseline CD4 count) as a measure to investigate the association of the extent of immune recovery and cancer risk. We evaluated whether nadir pre-ART CD4 count and change in CD4 count from baseline was associated with cancers overall and subgroups using multivariable Poisson regression adjusting for the same covariates.

Sensitivity analyses

Several sensitivity analyses were conducted: 1) lagging time-updated CD4 count by 6 or 12 months to account for potential reverse causation and CD4 count reductions leading up to a cancer diagnosis, 2) including only centrally validated cancer events, 3) including participants with cancers diagnosed prior to baseline, 4) using time-weighted average of area under time-updated CD4 count measurements curve using the trapezoidal rule[16], and 5) using complete case series analysis excluding participants with missing data on any variables.

All analyses were conducted using Stata/SE 18.0 (StataCorp LLC, College Station, TX, USA).

RESULTS

Baseline characteristics

We included 48,343 participants who achieved ≥2 years of virological suppression in analyses from 8 cohorts in D:A:D and 15 cohorts RESPOND from 37 countries (Supplementary Figure S1). Among them, 22,508 (46.6%) were from D:A:D only and 17,779 (36.8%) were from RESPOND only (8056 [16.7%] were enrolled in both cohorts). At baseline 74.4% were male, median age was 43 (interquartile range [IQR] 37, 50) years, median time since HIV diagnosis was 7.4 (3.3, 13.5) years, and median pre-ART nadir CD4 count was 245 (121, 394) cells/μL. Baseline demographic and clinical characteristics were similar between individuals included compared with those excluded in the final analysis (Supplementary Table S2).

A total of 1933 (3.9%) participants developed cancer during follow-up (Table 1). At baseline, participants with cancer were older (median 50 [IQR 44, 57] vs. 44 [37, 50] years), had similar median CD4 counts at baseline (517 [342, 716] vs. 540 [380, 730] cells/μL), but lower median pre-ART nadir CD4 (194 [80, 310] vs. 242 [120, 390] cells/μL).

Cancer incidence after two years of virological suppression

Over 300,273 person-years of follow-up (PYFU), 1933 (3.9%) participants developed cancer (incidence rate (IR) of 6.43 (95%CI 6.15, 6.73)/1000 PYFU) after ≥2 years of virological suppression. The median follow-up duration was 6.2 [IQR 2.9, 9.5] years for the total population, 6.1 [3.0, 9.6] years for participants without a cancer diagnosis and 4.2 [1.8, 7.1] years for those with a cancer diagnosis. There were 258 cases of ADC (0.5%), and 1675 cases of NADC (3.5%), with IRs of 0.86 (95%CI 0.76, 0.97)/1000 PYFU, and 5.58 (95%CI 5.31, 5.85)/1000 PYFU. There were 645 infection-related cancers (IR 2.22, 95%CI 1.98, 2.32/1000 PYFU), and 1288 infection-unrelated cancers (IR 4.29, 95%CI 1.06, 4.53/1000 PYFU). The most common cancers were lung cancer, anal cancer and prostate cancer, followed by non-Hodgkin's lymphoma and breast cancer (Supplementary Table S1). The crude incidence rate of cancers overall, cancer groups and individual cancers are presented in Figure 1, and the stratifications by age at baseline (≤50, 50), pre-ART nadir CD4 (<200, 200-350, >350 cells/μL) and race/ethnicity (White, Black, other, unknown) are presented in Tables 2 and Table 3.

Association between the recent CD4 count and cancer diagnosis

In multivariable Poisson regression, higher time-updated CD4 count was associated with a reduced risk of development of cancers overall (adjusted incidence rate ratio [aIRR] for time-updated CD4 350-499 cells/μL: 0.45 [95%CI 0.39, 0.51]; 500-749 cells/μL: 0.30 [0.27, 0.34], and ≥750 cells/μL: 0.26 [0.23, 0.30] compared with <350 cells/μL, p<0.0001) (Figure 2). A test for trend confirmed strong evidence of a linear association between increasing time-updated CD4 count and lower cancer risk (p-trend <0.001). There were no significant interactions between time-updated

CD4 count and age group (categorized as ≤50/>50 years) ($P_{interaction}$=0.24), sex ($P_{interaction}$=0.97) or calendar periods (<2015/≥2015) ($P_{interaction}$=0.40).

The results remained consistent for ADC (p<0.0001) and NADC (p<0.0001), although the strength of the association was smaller for NADC compared to ADC, and for infection-related and infection-unrelated cancers (Figure 2) as well as individual cancers except prostate cancer (Figure 3). The degree of cancer risk reduction with higher time-updated CD4 count is greater in infection-related cancer than infection-unrelated cancer, with a time-updated CD4 ≥750 cells/μL (vs. <350) being associated with an almost 90% reduction in infection-related cancers, whereas this reduction is lower (~60%) for infection-unrelated cancers. When ADC were excluded from the infection-related cancer group (n=444), time-updated CD4 counts remain associated with cancer incidence: 350-499 IRR: 0.30 [0.22, 0.39], 500-749 (0.15 [0.11, 0.20], and ≥750 (0.16 [0.12, 0.21], compared to <350 cells/μL.

In the adjusted analyses stratified by pre-ART CD4 nadir levels, associations between time-updated CD4 count (representing amount of immune recovery) and reduced risk for the development of cancers overall, ADC, NADC, infection-related, and infection-unrelated cancers were consistently observed across various pre-ART CD4 nadir groups (<200, 200-350, >350 cells/μL, p-values <0.0001) (Figure 4). The results were consistent with smoking-related and obesity-related cancers (Supplemental Figure S2). It is noteworthy that participants with higher pre-ART CD4 nadir also exhibited lower cancer risk, despite the observed significant protective associations across all groups (Figure 4).

As an indicator of immune recovery, we further investigated the association between the diagnosis of cancers and changes in CD4 count. In adjusted analyses, we found that an increase in CD4 count (per 50 cells/μL increase) was strongly associated with a reduced risk of incident cancers overall, cancer groups and individual cancers (Supplementary Table S3). Furthermore, pre-ART nadir CD4 was only associated with reduced risk of ADC and infection-related cancers but not for cancers overall and other cancer groups such as NADC, smoking- and obesity-related cancers (Supplementary Table S3).

Furthermore, we observed the diminished risk of overall cancers and specific cancer groups associated with higher time-updated CD4 count levels in both male and female subgroups, as well as in age subgroups categorized as ≤50 and >50 years (Supplementary Table S5). We examined the relationship between time-updated CD4 count categories and the development of most common individual cancers. The findings were consistent across all cancers assessed, including non-Hodgkin's lymphoma, lung cancers, liver cancers, breast cancers, and anal cancers, except for prostate cancer (p=0.745) (Figure 5). These associations persist across pre-ART nadir CD4 groups for most cancers, but only among those with low pre-ART nadir CD4 ≤200 cells/μL for breast cancers (Figure 5). Notably, the lower pre-ART nadir CD4 count was only associated with NHL but not with other cancers (Supplementary Table S4).

Sensitivity analyses

We conducted a series of sensitivity analyses to evaluate the robustness of our findings. We observed that a time-updated CD4 count lagged by 6 or 12 months was associated with a reduced risk of overall cancers and cancer subgroups and most common cancers, except prostate and breast cancers. (Supplementary Table S6 and S7). The associations between 6-month lagged CD4 and the reduced risk of cancer became weaker compared to the primary analysis. The results from sensitivity analyses remained consistent with the primary analysis across the various analyses. (Supplementary Table S6 and S7).

DISCUSSION

Using combined data from two large multinational HIV cohorts, we found poorer immune recovery despite sustained virological suppression to be associated with an increased incidence of cancers overall, common individual cancers, as well as the cancer groupings: ADC, NADC, infection-, infection-unrelated-, smoking- and obesity-related cancers. The associations remained consistent across various subgroups and sensitivity analyses, including those with low pre-ART nadir CD4. The reduced risk of cancer overall was also observed in participants with CD4 count ≥750 cells/μL, compared to those with CD4 count 500-749 cells/μL. These findings reinforce the importance of optimal immune recovery on the incidence of cancers in people with HIV.

Previous studies have established associations between low CD4 counts, prolonged immunosuppression or shorter durations of HIV virological suppression with development of both ADC and NADC.[6, 17] However, our study is the first to demonstrate a significant association between poor immune recovery with cancers overall, encompassing all cancer groups, in people with sustained virological suppression. In addition to the findings from previous studies,[11, 18, 19] which have shown a significant increase in the risk of ADC and infection-related cancers with HIV viremia, our study, by exclusively focusing on participants with at least two years of virological suppression, offers a robust understanding of the impacts of immune restoration on cancer incidence, unbiased by the influence of unsuppressed HIV VL.

Compared to a prior combined D:A:D/RESPOND analysis of cancer trends, we report lower incidence rate of ADC (1.94 vs. 0.86/1000 PYFU) and infection-related cancers (3.42 vs. 2.15/1000 PYFU) due limiting assessment to participants with sustained virological suppression. However, there were no differences in the incidence rates of NADC between the present and previous studies. This supports findings from previous studies of a greater impact of HIV viremia on ADC and infection-related cancers [17, 20]. However, there is contradictory evidence regarding the impact of HIV viremia on NADC risk. While a recent RESPOND analysis[21] and an earlier French study[22] have shown no association between HIV viremia and NADC, results from the Veterans Aging Cohort Study and a population-based study in the U.S., demonstrated an association between ongoing viral replication and NADC.[6, 18] The latter study also showed that

combining HIV VL and CD4 count measures provide a better risk prediction of NADC than either measure alone.[6]

When considering the most recent CD4 count prior to cancer diagnosis, a previous study demonstrated a significant, but low magnitude, decline in CD4 count leading up to cancer diagnosis.[23] Another study reported a meaningful CD4 decline (>15%) occurred in only 6 out of 87 cancer cases 6 months prior to cancer diagnosis. [24] This decline may be attributed to reductions in lymphocyte counts during the development of cancer. While our study primarily utilizes the most recent CD4 count, results were consistent when the analysis used a time updated CD4 count lagged by 6-12 months. There are also potential limitations in capturing the relationship between immune status and cancer development solely through this measure.

Consistent with previous studies, individuals with lower time-updated CD4 counts appear at higher risk of certain common cancers, including lung, anal, liver, NHL and breast, but not prostate cancer. Other immune measures such as cumulative duration of immunosuppression (CD4 <200 cells/μL) or lower nadir CD4 have been associated with an increased risk of both ADC and NADC.[21, 22, 25] In our study, a lower pre-ART nadir CD4 count was only associated with an increased risk of ADC and some infection-related cancers but not NADC and other cancer groups, suggesting a potential underlying mechanism specific to these cancer categories, possibly related to immune dysregulation and excess inflammation during the early untreated stages of HIV infection.[26]

Our study has several limitations including a relatively young cohort population and a median 6 years of follow-up. Study participants are mainly from Europe and Australia which may limit the generalizability to other regions. CD8 counts were largely missing in the D:A:D cohort, making the inclusion of CD4/CD8 ratio in assessing the relationship between poor immune recovery and cancer risk unfeasible. We also did not have information on cancer screening or family history. It also remains challenging to identify a single indicator that can comprehensively capture immune recovery after ART initiation. Despite these limitations, our findings, which demonstrate an association between a normalized immune response and a lower risk of cancer remain robust across various measures of CD4 count.

CONCLUSIONS

In this large cohort study integrating data from the D:A:D/RESPOND collaborations, individuals with suboptimal immune recovery experienced an increased risk of incident cancers despite achieving durable virological suppression. This highlights the critical importance of diagnosing HIV at the earliest opportunity, promptly initiating ART to ensure optimal immune recovery and sustained cancer risk reduction, and ensuring people with poor immune recovery despite effective ART undergo appropriate cancer screening strategies.

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Data sharing: The RESPOND Scientific Steering Committee (SSC) encourages the submission of concepts for research projects. Online research concepts should be submitted to the RESPOND secretariat (respond.rigshospitalet@regionh.dk); for guidelines of how to submit research concepts see the RESPOND governance and procedures at https://chip.dk/Portals/0/files/RESPOND/RESPOND%20governance%20and%20procedures_v6_2019SEP30.pdf?ver=2019%E2%80%9310%E2%80%9302%E2%80%93144419%E2%80%93230. The secretariat will direct the proposal to the relevant Scientific Interest Group, where the proposal will initially be discussed for scientific relevance before being submitted to the SSC for review. Once submitted to the SSC, the research concept's scientific relevance, relevance to RESPOND's ongoing scientific agenda, design, statistical power, feasibility, and overlap with already approved projects will be assessed. Upon completion of the review, feedback will be provided to the proposer or proposers. In some circumstances, a revision of the concept might be requested. If the concept is approved for implementation, a writing group will be established consisting of the proposers (up to three people who were centrally involved in developing the concept), representatives from RESPOND cohorts, and representatives from the Statistical Department and Coordinating Center. All individuals involved in the process of reviewing these research concepts are bound by confidentiality. All data within RESPOND from individual cohorts are de-identified. The present RESPOND data structure and a list of all collected variables and their definitions can be found at https://chip.dk/Portals/0/files/RESPOND/Study%20documents/RESPOND_EuroSIDA_SOP_Electronic_Version_7.0.pdf?ver=2023-07-18-150155-957&timestamp=1689685440820. For any inquiries regarding data sharing, please contact the RESPOND secretariat by email (respond.rigshospitalet@regionh.dk).

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Role of the funding source: As per RESPOND governance, funders of the study were also academic collaborators, and employees or associates could be included as co-authors if they met the International Committee of Medical Journal Editors criteria. However, funding bodies (including employees and associates hereof), were not in a position to veto study design, data collection, data analysis, data interpretation, or writing of the manuscript.

Ethics statement: Participants are consented to share data with RESPOND according to local requirements. Participants were pseudonymized at enrolment by assigning a unique identifier by the participating cohort before data transfer to the main RESPOND database. According to national or local requirements, all cohorts have approval to share data with RESPOND. Ethical approval was obtained, if required, from the relevant bodies for collection and sharing of data. Data are stored on secure servers at the RESPOND coordinating center in Copenhagen, Denmark, in accordance with current legislation and under approval by The Danish Data Protection Agency

(approval number 2012-58-0004, RH-2018-15, 26/1/2018), under the EU General Data Protection Regulation (2016/679).

All participating cohorts followed local or national guidelines or regulations regarding patient consent and ethical review. Of the countries with participating cohorts, only Australia and Switzerland require specific ethical approval for the entire D:A:D cohort in addition to that required for their national cohorts (the Australian HIV Observational Database and the Swiss HIV Cohort Study); France (Nice and Aquitaine cohorts), Italy (ICONA cohort), and Belgium (Brussels Saint-Pierre cohort) do not require specific ethical approval more than that required for the individual cohorts, and the Netherlands (AIDS Therapy in the Netherlands project) does not require any specific ethical approval, because data are provided as part of HIV care. For the EuroSIDA study, which includes the data from the Barcelona Antiretroviral Surveillance Study and Swedish cohorts, among participants from many European countries, each participating site has a contractual obligation to ensure that data collection and sharing are done in accordance with national legislation; each site's principal investigator either maintains appropriate documentation from an ethical committee (if required by law) or has a documented written statement to say that this is not required.

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D:A:D Participating Cohorts

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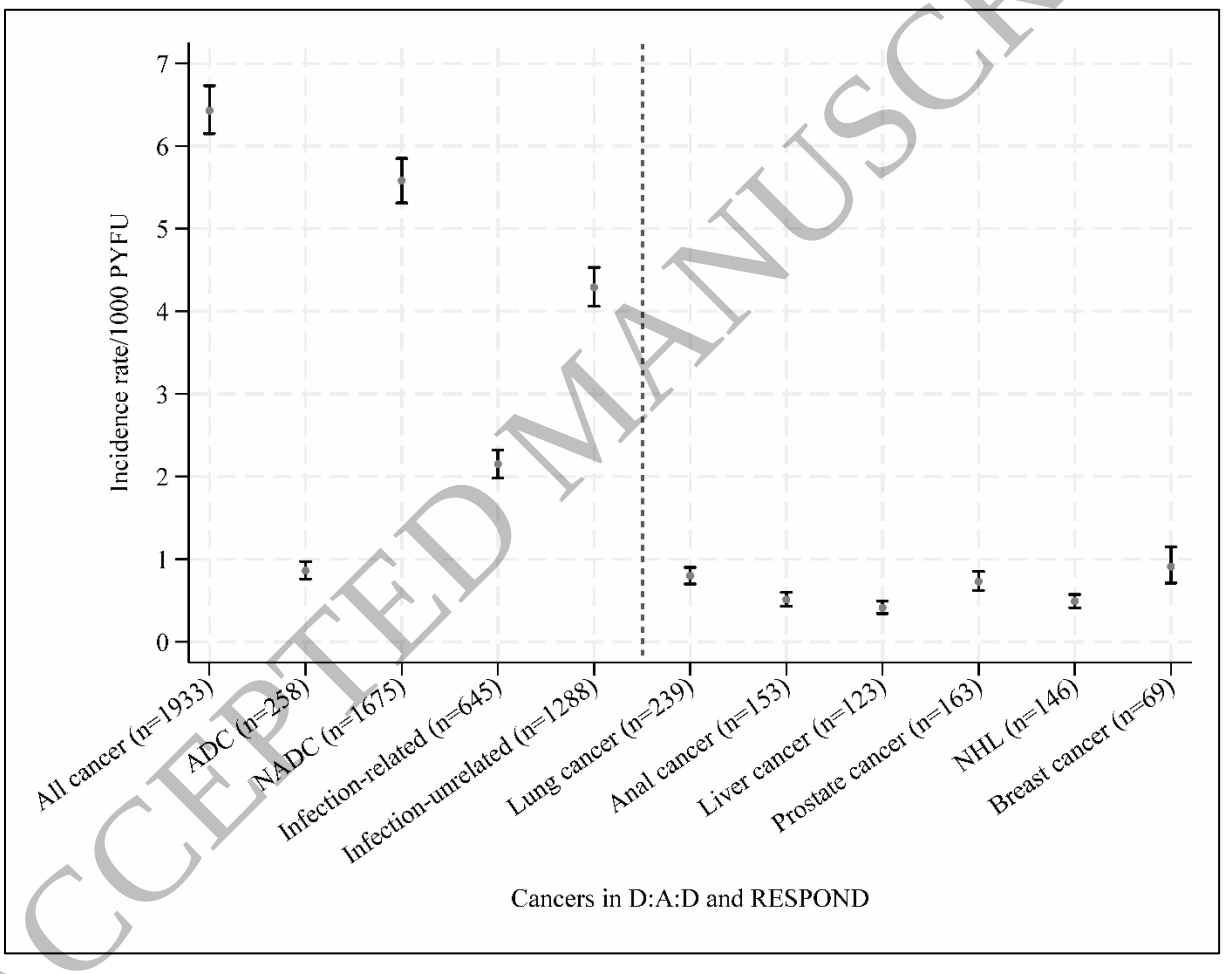
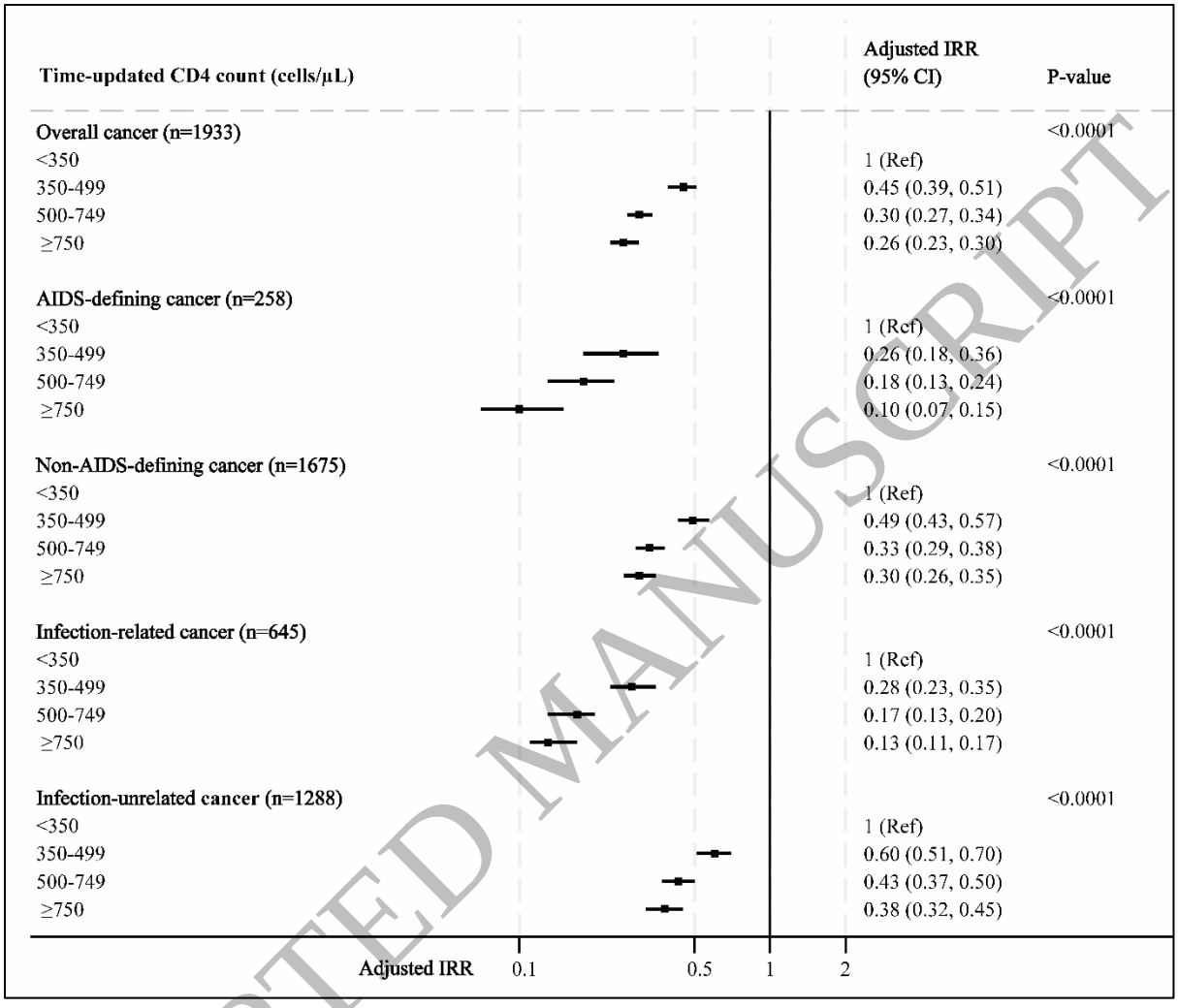
FIGURE LEGENDS

Figure 1. Cancer incidence after at least 2 years of virological suppression in D:A:D and RESPOND collaborations



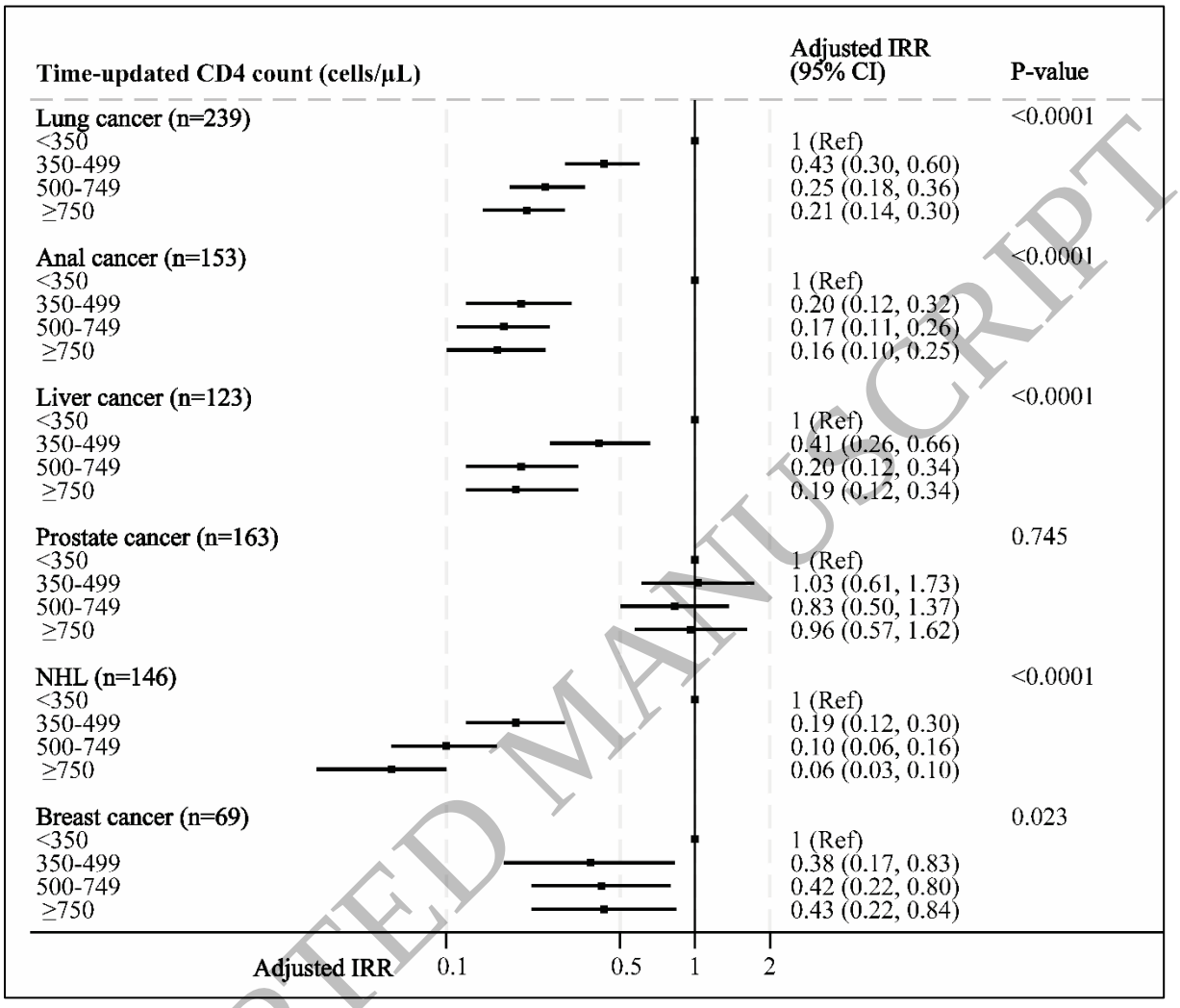
Cancer incidence rates on the left of the dotted line represent the overall cancer and cancer groups, while those to the right are individual cancer types.

Figure 2. Association between time-updated CD4 count and cancers overall and cancer groups



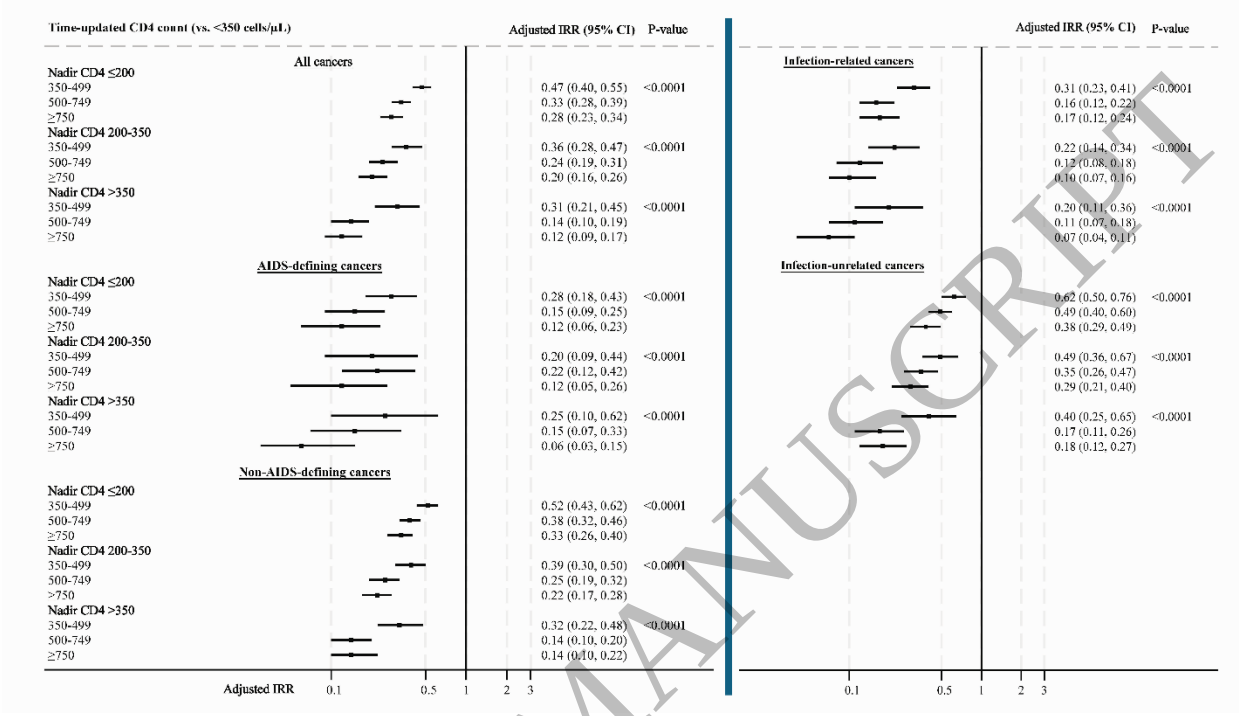
Poisson regression models for cancer overall and cancer groups were adjusted for sex, race/ethnicity, geographical region, HIV transmission risk group, duration since HIV diagnosis, a prior non-cancer AIDS event, HCV, HBV, BMI, hypertension, diabetes, CVD, chronic kidney disease, and dyslipidemia all fixed at baseline. Time updated covariates included age, smoking status, as well as any exposure to INSTIs, PIs, NRTIs, and NNRTIs (as cumulative exposure). Abbreviations: IRR, incidence rate ratio

Figure 3. Association between time-updated CD4 count and individual cancers



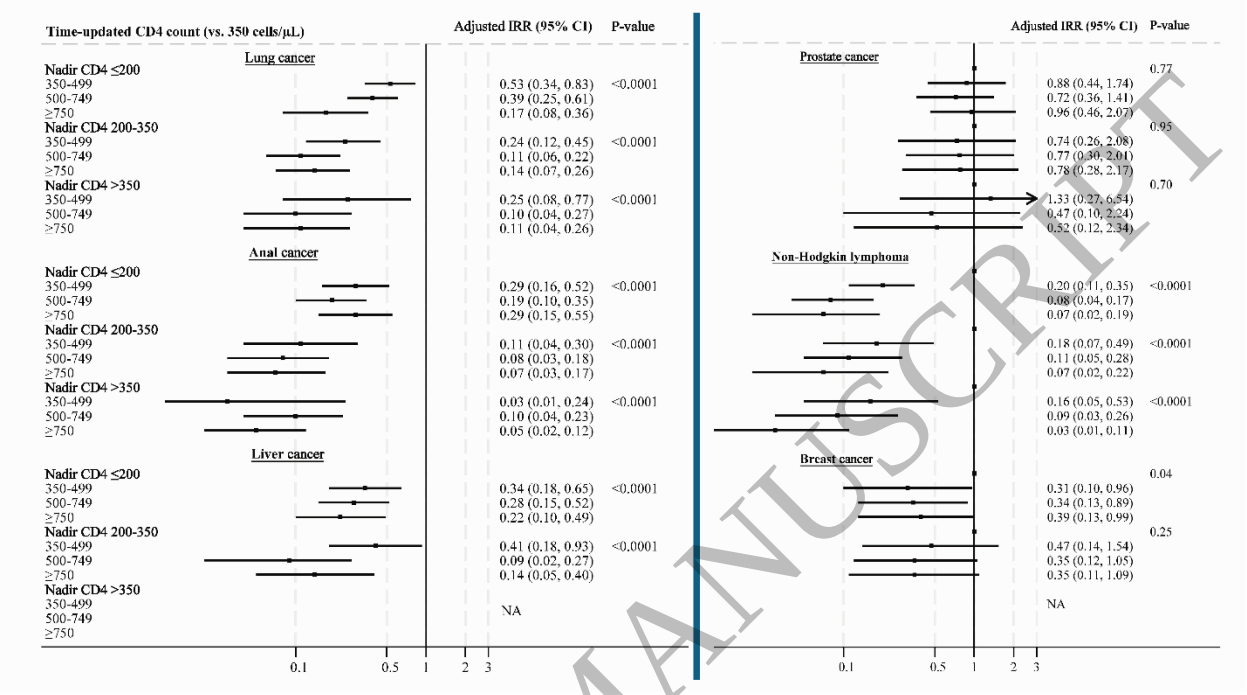
Poisson regression for all individual cancers were adjusted for sex, race/ethnicity, geographical region, HIV transmission risk group, and a prior non-cancer AIDS event all fixed at baseline. Time updated covariates included age and smoking status. Models for liver cancer were additional adjusted for HBV and HCV infection. Models for breast cancer included only females while models for prostate cancer included only males.
Abbreviations: IRR, incidence rate ratio; NHL, non-Hodgkin lymphoma.

Figure 4. Association between time-updated CD4 count and cancers overall and cancer groups, stratified by pre-ART nadir CD4 counts



Poisson regression models for cancer overall and cancer groups were adjusted for sex, race/ethnicity, geographical region, HIV transmission risk group, duration since HIV diagnosis, a prior non-cancer AIDS event, HCV, HBV, BMI, hypertension, diabetes, CVD, chronic kidney disease, and dyslipidemia all fixed at baseline. Time updated covariates included age, smoking status, as well as any exposure to INSTIs, PIs, NRTIs, and NNRTIs (as cumulative exposure). Abbreviations: IRR, incidence rate ratio

Figure 5. Association between time-updated CD4 count and individual cancers, stratified by pre-ART nadir CD4 counts



Poisson regression for all individual cancers were adjusted for sex, race/ethnicity, geographical region, HIV transmission risk group, and a prior non-cancer AIDS event all fixed at baseline. Time updated covariates included age and smoking status. Models for liver cancer were additional adjusted for HBV and HCV infection. Models for breast cancer included only females while models for prostate cancer included only males.

Abbreviations: IRR, incidence rate ratio; NHL, non-Hodgkin lymphoma.

Table 1. Participant characteristics of people living with HIV with or without overall cancer during follow-up at analysis baseline[$]

		Total (n=48,343)		Cancer during follow-up (n=1,933)		No cancer during follow-up (n=46,410)	
		n	%	n	%	n	%
Sex/Gender	Male	36,018	74.4	1,517	78.5	34,501	74.3
	Female	12,290	25.4	416	21.5	11,874	25.6
	Transgender	35	0.1	0	0.0	35	0.1
Race/Ethnicity	White	26,846	55.4	1,217	63.0	25,629	55.2
	Black	3,386	7.0	69	3.6	3,317	7.1
	Other	1,603	3.3	28	1.4	1,575	3.4
	Unknown	16,508	34.1	619	32.0	15,889	34.2
Geographical Region [a]	Western Europe	18,697	38.6	861	44.5	17,836	38.4
	Southern Europe	9,251	19.1	382	19.8	8,869	19.1
	Northern Europe	16,981	35.1	605	31.3	16,376	35.3
	Eastern Europe	3,414	7.0	85	4.4	3,329	7.2
Mode of HIV acquisition	MSM	22,133	45.7	863	44.6	21,270	45.8
	IDU	6,444	13.3	355	18.4	6,089	13.1
	Heterosexual	16,806	34.7	591	30.6	16,215	34.9
	Other	1,069	2.2	49	2.5	1,020	2.2
	Unknown	1,891	3.9	75	3.9	1,816	3.9
Smoking status	Never	11,944	24.7	375	19.4	11,569	24.9
	Current	18,060	37.3	872	45.1	17,188	37.0
	Previous	8,858	18.3	404	20.9	8,454	18.2
	Unknown	9,481	19.6	282	14.6	9,199	19.8
Body mass index (kg/m^2)	<18.5	1,833	3.8	105	5.4	1,728	3.7
	18.5-<25	24,879	51.4	1,016	52.6	23,863	51.4
	25-<30	2,850	5.9	90	4.7	2,760	5.9
	>30	10,587	21.9	431	22.3	10,156	21.9
	Unknown	8,194	16.9	291	15.1	7,903	17.0
Prior AIDS	No	39,666	81.9	1,446	74.8	38,220	82.4
	Yes	8,677	17.9	487	25.2	8,190	17.6
Hepatitis C [c]	No	3,729	7.7	122	6.3	3,607	7.8
	Yes	42,322	87.4	1,710	88.5	40,612	87.5
	Unknown	1,923	4.0	104	5.4	1,819	3.9
Hepatitis B [d]	No	4,098	8.5	119	6.2	3,979	8.6
	Yes	36,727	75.8	1,338	69.2	35,389	76.3
	Unknown	8,562	17.7	518	26.8	8,044	17.3
Hypertension [e]	No	3,054	6.3	77	4.0	2,977	6.4
	Yes	46,864	96.8	1,819	94.1	45,045	97.1
	Unknown	1,479	3.1	114	5.9	1,365	2.9

Diabetes [f]	No	36,018	74.4	1,517	78.5	34,501	74.3
	Yes	12,290	25.4	416	21.5	11,874	25.6
Cardiovascular disease	No	40,113	82.8	1,673	86.5	38,440	82.8
	Yes	1,125	2.3	85	4.4	1,040	2.2
	Unknown	7,105	14.7	175	9.1	6,930	14.9
Chronic kidney disease [g]	No	47,520	98.1	1,876	97.1	45,644	98.3
	Yes	279	0.6	32	1.7	247	0.5
	Unknown	544	1.1	25	1.3	519	1.1
Dyslipidaemia [h]	No	12,635	26.1	352	18.2	12,283	26.5
	Yes	35,708	73.7	1,581	81.8	34,127	73.5
Previous exposure to INSTI		5,177	10.7	110	5.7	5,067	10.9
Previous exposure to PI		28,602	59.1	1,401	72.5	27,204	58.6
Previous exposure to NNRTI		30,731	63.4	1,322	68.4	29,409	63.4
Previous exposure to NRTI		22,694	46.9	1,131	58.5	21,563	46.5
Continuous variables		**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**
Age, years		43	37, 50	50	44, 57	44	37, 50
CD4 nadir, cells/μL,[b]		245	121, 394	194	80, 310	242	120, 390
CD4 count at analysis baseline, cells/μL,[b]		540	380, 730	517	342, 716	540	380, 730
Duration since HIV diagnosis, years		7.4	3.3, 13.5	11.0	5.1, 17.2	7.5	3.4, 13.5

Abbreviations: MSM-men who have sex with men; IDU-intravenous drug user; ART-antiretroviral therapy; VL-viral load; cps-copies; AIDS, acquired immune deficiency syndrome; IQR-interquartile range; INSTI-integrase strand transfer inhibitor; PI-protease inhibitor; NRTI- nucleoside reverse transcriptase inhibitor; NNRTI-non-NRTI.

[$] Analysis baseline date was the first viral load <200 copies/mL (for more than 2 years) from the latest of study entry or 1 January 2006 in the D:A:D cohort, OR the latest of local cohort enrolment or 1 January 2012 for participants the RESPOND cohort.

[a] Due to small numbers, Australia was combined with Northern Europe, and Eastern Central Europe combined with Eastern Europe.

[b] CD4 count was taken as the most recent measurements in the 12 months prior to analysis baseline (i.e., the date of achieving >2 years of viral suppression). If no measurements were taken prior to analysis baseline, the first measurement within 12 weeks after analysis baseline was used. CD4 nadir was taken as the lowest CD4 cell count prior to ART initiation.

[c] Hepatitis C was defined by use of anti-HCV medication, a positive HCV antibody test, a positive HCV RNA qualitative test, HCV RNA-VL > 615 IU/mL, and/or a positive genotype test.

[d] Hepatitis B was defined by a positive HBV surface antigen and/or HBV DNA-VL > 357 IU/mL.

[e] Hypertension was confirmed by use of anti-hypertensives at any time before baseline, or if the most recent systolic or diastolic blood pressure measurement before baseline was higher than 140 or 90 mmHg, respectively.

[f] Diabetes was defined by a reported diagnosis, use of anti-diabetic medication, glucose ≥11.1 mmol/L, and/or HbA1c ≥ 6.5% or ≥48 mmol/mol.

[g] Chronic kidney disease was defined as two consecutive eGFR measurements <60 mL/min/1.73m^2 (calculating using the CKD Epidemiology Collaboration, CKD-EPI) measured at least 3 months apart. [h] Dyslipidaemia was defined as total cholesterol > 239.4 mg/dL or HDL cholesterol < 34.7 mg/dL or triglyceride >203.55 mg/dL or use of lipid-lowering treatments.

Table 2. Crude incidence rate of overall cancers and cancers subgroups

	All cancers		AIDS-defining cancers		Non-AIDS-defining cancers		Infection-related cancers		Infection-unrelated cancers	
	Number	**Incidence rate/1000 person-years (95% CI)**	**Number**	**Incidence rate/1000 person-years (95% CI)**	**Number**	**Incidence rate/1000 person-years (95% CI)**	**Number**	**Incidence rate/1000 person-years (95% CI)**	**Number**	**Incidence rate/1000 person-years (95% CI)**
Overall	1933	6.43 (6.15 6.73)	258	0.86 (0.76, 0.97)	1675	5.58 (5.31, 5.85)	645	2.15 (1.98, 2.32)	1288	4.29 (1.06, 4.53)
Sex/Gender										
Male	1517	6.76 (6.43, 7.11)	191	0.85 (0.73, 0.98)	1326	5.91 (5.60, 6.24)	526	2.34 (2.22, 2.56)	991	4.42 (4.15, 4.70)
Female	416	5.48 (4.97, 6.03)	67	0.88 (0.68, 1.12)	349	4.60 (4.12, 5.11)	119	1.57 (1.30, 1.88)	297	3.91 (3.48, 4.38)
Age at baseline, years										
≤50	946	4.24 (3.97, 4.52)	160	0.72 (0.61, 0.84)	786	3.52 (3.28, 3.78)	380	1.70 (1.54, 1.88)	566	2.54 (2.33, 2.76)
>50	987	12.7 (12.0, 13.6)	98	1.26 (1.19, 1.36)	889	12.7 (10.3, 12.3)	265	3.42 (3.02, 3.86)	722	9.33 (8.66, 10.03)
Pre-ART nadir CD4, cells/μL										
<200	985	7.40 (6.95, 7.88)	146	1.09 (0.93, 1.29)	839	6.31 (5.89, 6.75)	357	2.68 (2.41, 2.98)	628	4.72 (4.36, 5.11)
200-350	577	6.10 (5.61, 6.61)	59	0.62 (0.47, 0.80)	518	5.47 (5.01, 6.00)	163	1.72 (1.5, 2.01)	414	4.37 (3.96, 4.82)
>350	371	5.11 (4.60, 5.66)	53	0.73 (0.55, 0.96)	318	4.38 (3.91, 4.89)	125	1.72 (1.43, 2.05)	246	3.39 (2.98, 3.84)
Race/Ethnicity										
White	1217	7.04 (6.65, 7.45)	136	0.79 (0.66, 0.93)	1081	6.35 (5.89, 6.64)	377	2.18 (1.97, 2.41)	840	4.86 (4.54, 5.20)

Black	69	3.31 (2.57, 4.19)	14	0.67 (0.37, 1.13)	55	2.64 (2.00, 3.43)	23	1.10 (0.70, 1.65)	46	2.21 (1.61, 2.94)
Other	28	2.74 (1.83, 3.97)	8	0.79 (0.34, 1.54)	20	1.96 (1.19, 3.03)	9	0.88 (0.40, 1.67)	19	1.86 (1.12, 2.91)
Unknown	619	6.42 (5.93, 6.95)	100	1.04 (0.84, 1.26)	519	5.39 (4.93, 5.87)	236	2.45 (2.14, 2.78)	383	3.97 (3.59, 4.39)

Footnote: Cancer groups are not mutually exclusive since each cancer type could be included in more than one category

Table 3. Crude incidence rate of individual cancers

	Lung cancer		**Anal cancer**		**Liver cancer**		**Prostate cancer**		**Non-Hodgkin lymphoma**		**Breast cancer**	
	Number	**Incidence rate/1000 person-years (95% CI)**	**Number**	**Incidence rate/1000 person-years (95% CI)**	**Number**	**Incidence rate/1000 person-years (95% CI)**	**Number**	**Incidence rate/1000 person-years (95% CI)**	**Number**	**Incidence rate/1000 person-years (95% CI)**	**Number**	**Incidence rate/1000 person-years (95% CI)**
Overall	239	0.80 (0.70, 0.90)	153	0.51 (0.43, 0.60)	123	0.41 (0.34, 0.49)	163	0.73 (0.62, 0.85)	146	0.49 (0.41, 0.57)	69	0.91 (0.71, 1.15)
Sex/Gender												
Male	191	0.85 (0.74, 0.98)	135	0.60 (0.50, 0.71)	105	0.47 (0.38, 0.56)	163	0.73 (0.62, 0.85)	125	0.56 (0.46, 0.66)	NA	NA
Female	48	0.63 (0.47, 0.84)	18	0.24 (0.14, 0.37)	18	0.24 (0.14, 0.37)	NA	NA	21	0.38 (0.17, 0.42)	69	0.91 (0.71, 1.15)
Age at baseline, years												
≤50	84	0.38 (9.30, 0.47)	90	0.40 (0.32, 0.50)	68	0.31 (0.24, 0.39)	18	0.11 (0.06, 0.18)	83	0.37 (0.30, 0.46)	53	0.85 (0.63, 1.11)
>50	155	2.00 (1.70, 2.34)	63	0.81 (0.62, 1.04)	55	0.71 (0.54, 0.92)	145	2.26 (1.91, 2.66)	63	0.80 (0.63, 1.04)	16	1.20 (0.69, 1.95)
Pre-ART nadir CD4, cells/μL												

<200	124	0.93 (0.74, 1.11)	84	0.63 (0.50, 0.78)	75	0.56 (0.44, 0.71)	65	0.67 (0.54, 0.82)	89	0.67 (0.54, 1.15)	29	0.80 (0.54, 1.15)
200-350	78	0.82 (0.65, 1.03)	39	0.41 (0.29, 0.56)	31	0.33 (0.22, 0.46)	57	0.80 (0.61, 1.04)	31	0.33 (0.22, 0.46)	33	1.40 (0.96, 1.97)
>350	37	0.51 (0.36, 0.70)	30	0.41 (0.28, 0.59)	17	0.23 (0.14, 0.38)	41	0.73 (0.52, 0.98)	26	0.36 (0.23, 0.52)	14	0.87 (0.48, 1.47)
Race/Ethnicity												
White	148	0.86 (0.72, 1.01)	98	0.57 (0.46, 0.69)	84	0.49 (0.39, 0.60)	104	0.77 (0.63, 0.93)	84	0.49 (0.39, 9.60)	39	1.32 (0.98, 1.74)
Black	1	0.05 (0.001, 0.27)	1	0.05 (0.001, 0.27)	3	0.14 (0.03, 0.42)	2	0.10 (0.01, 0.35)	6	0.29 (9.11, 0.63)	4	0.19 (0.05, 0.49)
Other	5	0.49 (0.16, 1.14)	0	0	0	0	2	0.20 (0.03, 0.71)	4	0.39 (0.11, 1.00)	3	0.29 (0.06, 0.86)
Unknown	85	0.88 (0.70, 1.09)	54	0.56 (0.42, 0.73)	36	0.37 (0.26, 0.52)	55	0.57 (0.43, 0.74)	52	0.54 (0.40, 0.71)	23	0.24 (0.15, 0.36)